Computed tomography perfusion imaging of colorectal cancer in correlation with tumor grades

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Objective
Preoperative evaluation of tumor grading has essential implications in the treatment and prognosis in patients with colorectal cancers (CRCs). The aim of this study was to find the correlation between computed tomography (CT) perfusion parameters of CRC and each grade of it and the determination of the most important predictive parameters of CT perfusion for poorly differentiated CRCs.

Patients and methods
The study included 51 patients with colorectal carcinoma, pathologically proven by endoscopic biopsy. The patients underwent CT perfusion using a 16-row CT scanner. Quantitative values for blood flow, blood volume, mean transit time, and permeability surface were determined. Then the correlation between CT perfusion parameters and postoperative histopathological tumor grades was evaluated.

Results
Among CT perfusion parameters, there were significant differences in blood flow and blood volume between well-differentiated, moderately, and poorly differentiated CRCs (83.77±17.29 ml/100 g/min, 98.80±34.07 ml/100 g/min, 48.50±22.29 ml/100 g/min) and (7.20±2.32 ml/100 g, 7.44±3.73 ml/100 g, 4.62±3.03 ml/100 g), respectively. There were no significant differences as regards other perfusion parameters.

Conclusion
Among CT perfusion parameters, blood flow and blood volume can be used as predictive parameters for CRC grading. They show significantly lower values in poorly differentiated CRCs than in moderately differentiated and well-differentiated CRCs.

Keywords:
blood flow, computed tomography perfusion, poorly differentiated colorectal cancers

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Introduction

Colorectal cancer (CRC) is the third most common malignant tumor and the fourth leading cause of cancer deaths worldwide [1–4].

Tumor differentiation is an important prognostic factor of CRC. Poorly differentiated tumors have a worse prognosis than well-differentiated and moderately differentiated ones [5]. Poorly differentiated CRCs are usually associated with intestinal penetration, lymph node involvement, and vascular invasion, which is a risk factor for CRC spread [6].

The 5-year survival rate depends on the tumor stage and grade at the time of presentation and so treatment strategy based on the tumor stage and grade should be applied from the time of presentation to improve prognosis. Poorly differentiated CRCs are likely associated with venous invasion [7,8] which is a high-risk factor determining the use of adjuvant chemotherapy [9,10] and therefore preoperative grading of CRC is essential. Diagnosis of CRC is usually based on invasive colonoscopy, which allows direct visualization of the tumor and biopsy. However, the preoperative colonoscopic biopsy may fail to grade the cancer because of insufficient tissue specimens [11].

Computed tomography (CT) perfusion is a novel promising technique for the evaluation of tumor vasculature that depends on the temporal changes in tumor enhancement after intravenous contrast administration [12–14]. Clinical application of CT perfusion in oncology is increasingly reported in the literature [15,16].

Few studies have been conducted on the relationship between CT perfusion parameters of CRC and tumor grades [17]. Kim *et al.*[17] have reported that blood flow was significantly lower in poorly differentiated

than well-differentiated and moderately differentiated CRCs. Sun *et al.*[11] have reported that blood flow and blood volume in the well-differentiated CRC group were significantly higher than those in moderately and poorly differentiated groups.

Indeed, the debate continues regarding the correlation between CT perfusion parameters of CRC and tumor grades, so further investigation is required in this field of research.

The aims of this study were to determine the correlation between CT perfusion parameters for CRC and tumor grades and the determination of the most important predictive parameters of CT perfusion for poorly differentiated CRCs.

Patients and methods

This study was done in South Egypt Cancer Institute between January 2018 and December 2018 and included 51 patients with pathologically proven colorectal carcinomas by endoscopic biopsy. The following cases were excluded from the study: colorectal masses pathologically confirmed to be benign, patients who received preoperative neoadjuvant chemotherapy or radiotherapy, pregnant patients, those with raised renal chemistry, and hypersensitivity to contrast. We have got an approval from the Ethics Committee at Faculty of Medicine, Assiut University, number 17100795.

Sample size calculation

Sample size was calculated by G Power software (Chicago, Illinois USA) as a total of 50 cases, with an α error probability of 5% and confidence interval of 95%. As the aim of the study is to assess tumor perfusion, we used the mean values of blood volume of different grades of CRC for calculation of the sample size. The sample size was calculated for one-tailed statistical analysis.

CT technique

CT scans were performed using the GE Bright Speed (16 Row) CT scanner. Colonic dilatation by saline enema was done immediately before imaging and then precontrast scans were obtained in all patients to identify the colorectal tumor location, then 80 ml of iopromide (Ultravist; Schering, Berlin, Germany) was injected intravenously at a rate of 4 ml/s via an automatic pump injector for dynamic perfusion CT scans. Dynamic perfusion CT scans were performed at the mid-portion of the tumor for 60 s beginning 7 s after contrast injection.

Image analysis

All CT scanning data were sent to workstation GE AW 4.6. The CT perfusion body tumors protocol was used, and the deconvolution analytic method was the kinetic model used to calculate the perfusion parameters. The Arterial input was defined using the mouse to place a circular region of interest (ROI) on the aorta or common iliac artery of size less than 30 mm^2 with a mean surface area of 24.89 mm^2 and then the arterial time–density curve was obtained; then the tumor ROI was placed on the most enhanced bulky part of the tumor more than 90 mm^2 according to the tumor size with a mean surface area of 156.8 mm^2; subsequent to this the following perfusions parameters were calculated: blood flow, blood volume, mean transit time, and permeability surface.

Histopathological assessment

All the tumors underwent postoperative histopathological assessment and were classified into well-differentiated, moderately differentiated, or poorly differentiated colorectal adenocarcinoma. Then these results correlated to CT perfusion parameters.

Statistical analysis

Data were collected and analyzed using SPSS (the Statistical Package for the Social Sciences, version 20; IBM, Armonk, New York, USA). Continuous data were expressed in the form of mean ± SD or median (range), while nominal data were expressed in the form of frequency (percentage).

Analysis of variance was used to compare different perfusion parameters based on the grades of CRC. The level of confidence was kept at 95%. A P value less than 0.05 was considered significant.

Results

The mean age of patients was 53.87 ± 16.13 years, with a range between 19 and 86 years. Out of the studied patients, 26 (51%) patients were men, and 25 (49%) patients were women.

The most frequent presentations were constipation (51%) and abdominal pain (47%), followed by bleeding per rectum (19.5%) (Fig. 1).

The most frequently affected sites were rectum (41.5%) and sigmoid colon (17.6%), followed by rectosigmoid colon (9.8%) (Fig. 2).

By histopathological study, out of the studied patients, 11 (21.6%), 23 (45.1%), and 17 (33.3%) patients

had well-differentiated, moderately, and poorly differentiated adenocarcinoma, respectively (Figs. 3–5).

By the correlation between CT perfusion parameters and tumor grades, it was noticed that both blood flow and blood volume were significantly lower in poorly differentiated in comparison to moderately and well-differentiated CRCs, while other CT perfusion parameters of CRC showed insignificant differences between different grades (Table 1).

The diagnostic performance of blood flow and blood volume in diagnosing each grade of CRCs was assessed using receiver operating characteristic curves. It was noticed that for diagnosing poorly differentiated adenocarcinoma, the blood flow at a cutoff point less than 68.45 ml/100 g/min had 94% sensitivity and 85% specificity while the blood volume at a cutoff point less than 4.27 ml/100 g had 65% sensitivity and 91% specificity (Table 2).

Discussion

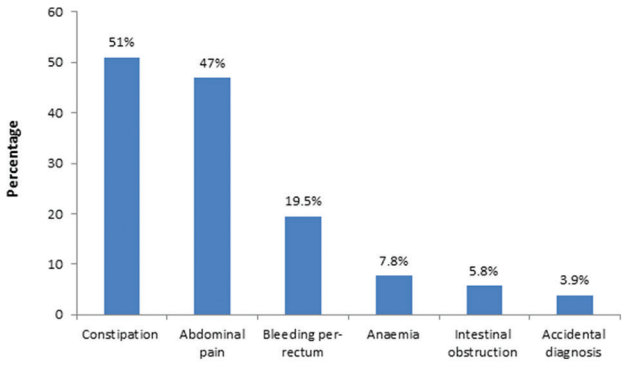
The importance of the preoperative diagnostic evaluation and grading of CRC is well established.

CT perfusion is a novel noninvasive imaging technique that can help in predicting tumor grade. Our results showed that among the four perfusion parameters, there were significant differences of the mean blood flow and blood volume values in different tumor grades.

The mean blood flow values were significantly lower in poorly differentiated CRCs than in moderately and well-differentiated CRCs.

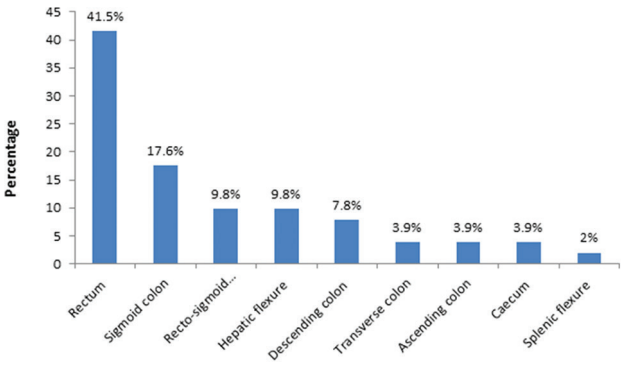
These results agreed with those reported by Kim *et al.*[17] Also, we agreed with Sun *et al.*[11] in that the blood flow values were the lowest in poorly differentiated CRCs; however, in contrast to our study Sun *et al.* reported that the blood flow values were significantly higher in well-differentiated than in moderately differentiated CRCs. Two reasons might have led to different results in different studies. First, the relatively smaller sample size used by Sun *et al.* [11].

Figure 1



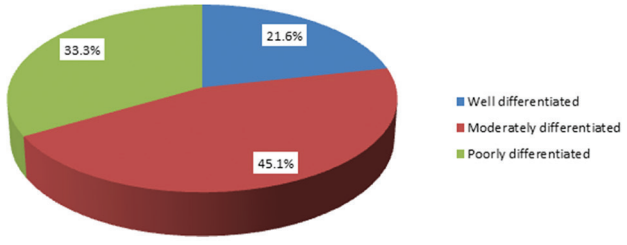
Presentations of patients in this study.

Figure 2



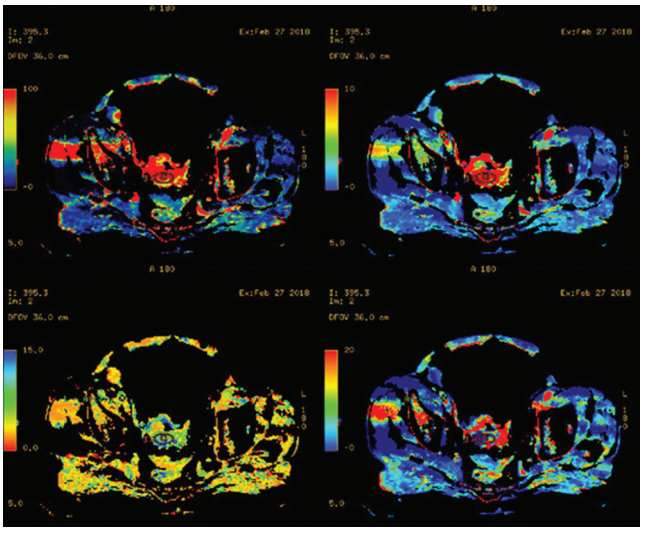
Site of colorectal cancer in this study.

Figure 3



Grades of tumor in the study.

Figure 4



A male patient of 67 years old presented with acute intestinal obstruction in the clinic of surgical oncology by. Noncontrast multislice computed tomography of the pelviabdomen revealed a sigmoid colonic mass measuring ± 2.7 × 4.4 cm in axial dimensions; postoperative histopathological assessment showed moderately differentiated adenocarcinoma. The predominant color in blood flow and blood volume color maps is red, suggesting high blood flow and blood volume values. The mean transit time and permeability surface maps show no significant differences between different tumor grades.

Table 1 Correlation between computed tomography perfusion parameters and tumor grade

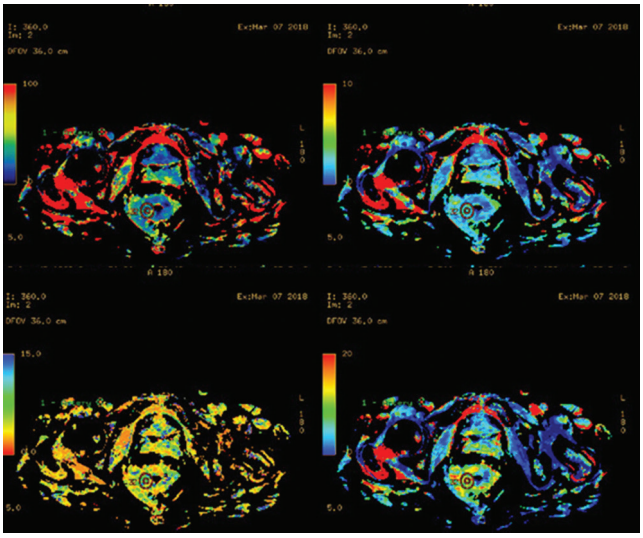
	Well differentiated	Moderately differentiated	Poorly differentiated	*P*
Blood flow (ml/min)	83.77±17.29	98.80±34.07	48.50±22.29	**<0.001**
Blood volume (ml)	7.20±2.32	7.44±3.73	4.62±3.03	**0.02**
Transit time (s)	7.51±2.11	6.23±2.26	7.23±1.79	0.17
Permeability area (ml)	12.15±7.26	11.10±6.13	11.13±4.17	0.87

Table 2 Diagnostic performance of blood flow and volume in diagnosing each grade of CRCs

	Poorly differentiated (%)		Moderately differentiated (%)		Well differentiated (%)	
	Blood flow	Blood volume	Blood flow	Blood volume	Blood flow	Blood volume
Sensitivity	94	65	73.9	91	90	90.9
Specificity	85	91	85.7	43	50	52.5
Positive predictive value	76	79	81	57	33	33.3
Negative predictive value	97	84	82	86	95	95.2
Cutoff point	<68.45	<4.27	>85.2	>4.27	>68.5	>5.29
Area under the curve	0.89	0.77	0.81	0.65	0.64	0.64
P	<0.001	<0.001	0.03	0.08	0.03	0.78

P value was significant if<0.05.

Figure 5



A female patient of 58-year old presented with chronic constipation, abdominal pain, and bleeding per rectum to the clinic of surgical oncology. Noncontrast multislice computed tomography of the pelviabdomen showed an anorectal mass measuring ± 4.2 × 3.4 cm in axial dimensions and postoperative histopathological assessment showed poorly differentiated adenocarcinoma. The predominant color in blood flow and blood volume color maps is blue, suggesting low blood flow and blood volume values. The mean transit time and permeability surface maps show no significant differences between different tumor grades.

Second, the different software applications do not seem to produce comparable quantitative perfusion results [18].

Kim *et al.*[17] assumed two hypotheses that account for low blood flow values in poorly differentiated CRCs. First, the growth rate of poorly differentiated CRCs is too rapid to develop angiogenesis of mature vessels. Second, poorly differentiated CRCs have more extensive areas in which endothelial cells have high vascular permeability, therefore the interstitial pressure increases and compresses the small capillaries more than in well-differentiated and moderately differentiated CRCs [11,17].

The mean blood volume values were significantly lower in poorly differentiated CRCs than in moderately and well-differentiated CRCs. These results agreed with Sun *et al.*[11] who used ROI outlining the tumor and reported that the blood volume in poorly differentiated CRCs were significantly lower than in well-differentiated CRCs.

As there were statistically significant differences in blood flow and blood volume values among different grades, the diagnostic performance of blood flow and blood volume was assessed using receiver operating characteristic curves. For diagnosing poorly differentiated adenocarcinomas, the blood flow cutoff value was less than 68.45 ml/100 g/min while the blood volume cutoff value was less than 4.27 ml/100 g.

In comparison to our study, Sun *et al.*[11] reported a lower blood flow cutoff value of 21.49 ml/100 g/min in diagnosing poorly differentiated adenocarcinomas. Two reasons can give explanation for these different results. The first reason is the influence of the difference in ROI size and position used in each study on the perfusion parameters. In our study, we used ROI placed on the most enhanced area of the tumor of surface area greater than 90 mm^2 with a mean surface area of 156.8 mm^2, while Sun *et al.* used ROI outlining the tumor [11]. This difference occurs because vascularity decreases from the tumor edge to the center, and the tumor center is less vascularized than the periphery [19]. The second reason is the relatively smaller number of poorly differentiated CRCs included by Sun *et al.*[11] that can contribute to the interpretation of this difference.

There were some limitations to our study. First, the CT scans were performed using a 16-row CT scanner, so perfusion scan was performed on just 2 cm thickness of the tumor, not whole-tumor perfusion. However, we tried to overcome this problem, by performing the perfusion scans on the most bulky part of the tumor.

Second, the acquisition effects caused by breathing motion artifacts; we tried to reduce these effects by asking the patients to hold the breath for 1 min during CT perfusion scans [20].

Third, the tumor ROI in CT perfusion may not be correlated with the postoperative pathologic specimen accurately; the use of the large ROI placed on the main bulk of the tumor reduced this effect.

Fourth, radiation dose remains a limitation in CT perfusion. However, as CT machines' hardware and software are developed and additional research is performed, the radiation dose of CT perfusion in patients may decrease significantly.

Conclusion

Among CT perfusion parameters, blood flow and blood volume can be used as predictive parameters for CRC grading. They show significantly lower values in poorly differentiated CRCs than in moderately differentiated and well-differentiated CRCs.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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